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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/416,812	10/13/99	RAMACHANDRA	M	CJ-0926KUS

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EXAMINER	
SORBELLO,E	
ART UNIT	**PAPER NUMBER**
1633	8

DATE MAILED: 11/13/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File Copy

Office Action Summary	Application No.	Applicant(s)	
	09/416,812	RAMACHANDRA ET AL.	
	Examiner	Art Unit	
	Eleanor Sorbello	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *16 August 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. Applicant's response to first office action on merits has been filed on 08/16/00 and entered as Paper No. 7. Claims 1-40 are pending in the present application.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the construction of a selectively replicating adenoviral vector comprising a TGF-β pathway responsive promoters (such as PAI-1 promoter and SRE-promoter) and p53 pathway responsive promoters (such as p53CON and RGC) operably linked to a repressor of viral replication, does not reasonably provide enablement for the (1) construction of any viral vector comprising pathway responsive promoters operably linked to a repressor of viral replication or (2) pharmaceutical compositions comprising any viral vector and (3) methods of killing cells *in vivo* or *ex vivo* by contacting target or host cells with the aforementioned recombination viral constructs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to (1) any selectively replicating recombinant virus comprising a pathway responsive promoter operably linked to a repressor of viral

replication, wherein the pathway responsive promoter is selected from either the p53, or Rb or TGF-β pathway, wherein the virus is an adenovirus; wherein the repressor of viral origin is E2F-RB; (2) pharmaceutical compositions comprising the aforementioned viruses; (3) *in vivo* methods of killing cells with a pathway defect by contacting the target cell with the recombinant virus of the instant application wherein the vector is administered intraperitoneally, intravenously or by intratumoral injection, and wherein the tumor cells are eliminated from stem cell products.

The specification teaches the construction of luciferase plasmids with TGF-beta-responsive promoters such as PAI and SRE, and p53-responsive promoters such as RGC and p53CON and plasmids comprising E2F-Rb. The specification teaches the construction of adenoviral vectors comprising PAI-Ad, SRE-Ad, RGC-Ad and CON-Ad containing E2F-Rb under the control of pathway-responsive promoter and GFP under the control of a CMV promoter flanked by Ad5 sequences. The specification also details the construction of specified adenoviral vectors of serotype 5 comprising the MLP promoter sequence comprising deletions in the E3 region and E1 region.

In view of the claims drawn to methods as in claims 29-33 which are directed to *in vivo* methods of killing cells with any viral vector comprising a pathway responsive promoter operably linked to a repressor of viral replication and also the pharmaceutical compositions as claimed in claims 14-28 comprising the viral vectors of the instant application, whereby DNA encoding genes responsible for the p53, Rb or TGF-beta pathways are manipulated via the viral vectors, the claims read on gene therapy applications.

The specification prophetically considers the administration of any selectively replicating viral vector to host cells wherein the p53 or Rb or TGF-beta pathway is defective. There is no specific teaching which indicates applicants are enabled for *in vivo* methods which include the administration of the adenoviral vector or any viral vector to a host cell other than *in vitro* cell culture. The claims also read on the transfer of an additional transgene via a vector. These methods read specifically on gene therapy where a gene is administered to therapeutically modify the existing gene in addition to modulating the p53, Rb or TGF-beta pathway of the individual thereby producing a phenotypic change or response. However the results do not indicate that any viral vector comprising the pathway responsive promoter linked to the repressor of viral replication and a transgene in an adenoviral vector with an E3 and/or E1 deletion was administered to a model animal to alleviate symptoms of a disease, due to defects in the p53, Rb or TGF-beta pathway.

Dang et al. in 1999, in a report summarizing the status of gene therapy, found human gene therapy to be an immature science with limited understanding of gene regulation and disease models for preclinical studies. (see page 471, paragraph 1). They also noted that it is not possible to predict results from one animal model to another, as was seen in experiments with nude mice and that with dogs. (see page 471, col. 2 , paragraph 2). Dang et al. also noted the major challenge in gene therapy is achieving efficient gene delivery to target tissues.

Eck et al. taught that the delivery of recombinant DNA has been a central issue in gene transfer *in vivo* . For instance, numerous factors complicate the art of gene

delivery *in vivo* which have not been shown to be overcome by routine experimentation. Eck et al. explains, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.); the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced; the stability of the mRNA produced, the amount and stability of the protein produced; and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically, based on the vector used, the protein being produced, and the disease being treated. [See Eck et al., ¶ bridging pages 81-82.]

None of these unpredictable factors discussed by Dang and Eck were specially addressed in applicant's disclosure. The instant specification does not teach the site of delivery, composition and quantities of the adenoviral vector used to be able to measure the effects of the administration of any viral vector except by prophetic consideration. Further it is unclear that from the cell culture example which indicates the multiplying capacity of the defective adenovirus in normal cells versus tumor cells having defective p53 and Rb pathways, wherein the p53 and Rb pathways are restored in the tumor cells due to the muliplying capacity of the adenoviral vector, that one could support the broad claims directed to any viral vector administered *in vivo* or *ex vivo*, in view of the unpredictability in the art.

In view of this, it would require undue experimentation for one skilled in the art to be able to practice the claimed invention of administering any viral vector comprising a

p53 or Rb or TGF-beta pathway responsive promoter *in vivo* such as eliminating tumor cells from stem cell products. Since, one skilled in the art cannot readily anticipate the results predicted for the *in vivo* or *ex vivo* context to which the claimed invention pertains based on the guidance provided in applicant's disclosure, one skilled in the art would necessarily consider such subject matter to be unpredictable.

Regarding claims 1-13 drawn to any viral vector comprising a pathway responsive promoter, the specification lacks guidance as to the breadth of the claims regarding any selectively replicating recombinant virus comprising a pathway responsive promoter. No other vectors are described with any particularity. Due to the unpredictability of gene therapy, particularly including efficient delivery, particular guidance regarding construction of the vector is required. Robbins et al. in his review in 1998, (see abstract), teaches the specific advantages and disadvantages that make different viral vectors suitable for particular gene-therapeutic applications.

The pharmaceutical composition claims 14-28 are not enabled for use because the language "pharmaceutical" implies that the vector of the claims provides for *in vivo or ex vivo* applicability particularly for treatment, but such is not enabled as is argued herein.

Therefore, considering the broad claims drawn to methods of killing a cell with a pathway defect by the administration of any viral vector comprising a pathway responsive promoter operably linked to a repressor of viral replication, wherein the method is practiced *in vivo* and the vector being administered intraperitoneally, intravenously or intratumorally, or *ex vivo* to eliminate tumor cells from stem cell

products, the specification is enabled for *in vitro* cell culture only and is not enabled for all aspects of *in vivo or ex vivo* mentioned previously. In order for one skilled in the art to practice the invention as claimed one would have to engage in undue experimentation in order to be able to administer any gene in the construct of the instant invention via any route of administration, and in a composition that has not been specified, to be able to measure the effects such as elimination of tumor cells from stem cell products, by the administration of any viral vector.

In conclusion, given the nature of the invention, the state of the art, the demonstrated lack of predictability of the art, the lack of guidance set forth, the breadth of the claims, the quantity of experimentation required, one of skill in the art could not use the invention *in vivo* or *ex vivo* in the specified context without undue experimentation.

4. Applicant's arguments filed 08/16/00 have been fully considered under 35 U.S.C. 112, first paragraph, but they are not found persuasive, as explained above. In summary, applicant's arguments under 35 U.S.C. 112 first paragraph wherein *in vivo* methodology is claimed by the extrapolation of results from *in vitro* cell culture, and not from art accepted models, is not persuasive due to the unpredictability of the art.

In the applicant's summary applicant refers to the complex art with which the invention deals with and applicant believes that he has satisfied the burden of demonstrating that the claims are enabled in accordance with 35 U.S.C. 112 first paragraph.

To reiterate, 35 U.S.C. 112 first paragraph states that the specification should contain detailed methods of making and using the invention, in a clear and concise manner in exact terms so as to enable any person skilled in the art to make and use the invention, and shall set forth the best mode contemplated by the invention in carrying out the invention.

As stated above in the statement of rejection, the state of the art with its high level of unpredictability does not enable a person skilled in the art to be able to practice the invention without undue experimentation. The specification must teach that that is not know in the art. As such, as explained above, extrapolation of *in vitro* cell culture would not be representative of *in vivo* gene transfer in studying the effects of the administration of DNA via any selectively replicating viral vector on elimination of tumor cells.

5. In reference to applicant's traversal regarding claims 14-36 rejected under 35 U.S.C. 112, first paragraph referencing (1) pharmaceutical formulations, (2) method of using (3) transformed cell with viral vector (4) claims directed to pathway responsive promoters, the following response is filed.

(1) As mentioned in the detailed rejection under 112 first paragraph, above and in the applicants traversal, applicant's state that pharmaceutical formulations are known in the art. Applicant's state that it would be unduly burdensome to recite the variety of formulations used for more than 40 yeafs in the field of vaccines. However, "pharmaceutical compositions" imply that the composition is to be used to provide

therapy. As mentioned in the body of the rejection under 112, first paragraph, of this office action, there is no specific teaching in the specification that indicates applicants admininstered a pharmaceutical composition comprising a specified viral vector into an art accepted model and attained a therapeutic response. Dang et al. in his review (1999) taught the unpredictability of the science of gene therapy as exemplified in the pioneering work of Anderson and Blaese (see page 471, paragraph 2 and 3). In their work, the transduction of the ADA gene into the lymphocytes of patients afflicted by immunodeficiency was shown but the data did not indicate therapeutic results. Hence as taught by Dang et al., this exemplifies the fact that scientific principles are not necessarily extrapolatable to *in vivo* results.

(2) As regards the methods of use claims 29-33, the claims are directed to a method of killing a cell with a viral vector comprising a pathway responsive promoter of the instant invention. Applicant directs his rebuttal against the FOAM, with regards to (a) dosing regimens (b) identification of appropriate target cells, (c) construction of adenoviral vectors comprising an E1 deletion; (d) combination chemotherapy treatment regimens; (e) construction of pathway responsive promoters; (f) use of immunosuppressive agents to mitigate an immune response; (g) ex-vivo stem cell purging protocols; (h) construction of PCR reagents and (I) Use of vectors would be unpredictable.

(a)As regards dosing regiments, applicant states that significant scientific literature exist for the care and treatment of cancer for the administration of recombinant viral vectors by physician sponsored INDs. However, it is not clear how one dosing

regimen for a specified viral vector is indicative of the dosing regimens for any viral vector for the treatment of any disease caused by a pathway defect, without the skilled artisan being engaged in undue experimentation.

Applicant refers to Table 1, in which 15 tumor cell lines developed from cell types defective in the p53 pathway and Table 2 which indicates that 6 different tumor cell lines defective in TGF-beta pathway, and the ability of the vectors of the present invention to selectively infect and replicate. However, it is not clear how one skilled in the art could anticipate the results of *in vivo* application without undue experimentation because of the unpredictability in the art.

(b) With regards to identification of appropriate target cells, applicant is enabled for identifying target cells having a pathway defects such as p53 and TGF-beta, with pathway responsive promoters such as PAI-1, SRE, p53CON and RGC. The vectors have been demonstrated to selectively replicate *in vitro* cell culture. However, as mentioned above, it is not clear how *in vitro* cell culture is representative of *in vivo* results.

(c) Applicant is enabled for the construction of adenoviral vectors comprising E1 deletions. However, the use of such vectors as instantly claimed remains at issue.

(d) With regards to combinational chemotherapy treatment regimens applicant states that protocols exist in the literature for the administration of recombinant adenoviral vectors in combination with anticancer drugs. Applicant prophetically states that any viral vector can be administered similarly and similar results obtained. However, as stated by Robbins in his review in 1999, these viral vectors have a number

of specific advantages and disadvantages that make them suitable for specific gene therapy applications.

(e) Applicant has described the construction of various pathway responsive promoters which are known in the art. However, applicant has not taught how to use the promoters described in specified vectors *in vivo* resulting in therapeutic results.

(g) Regarding applicant's rebuttal on ex vivo methodology, applicant states that the specification gives guidance regarding the use of viral vectors in ex vivo stem cell protocols. However, applicant did not disclose in the specification that the viral vectors of the instant invention were transfected into stem cells which were subsequently re-introducted into an art accepted model that indicated amelioration of a disease or condition. Due to the state of the art and its high level of unpredictability one cannot extrpolate these results to the claims.

(h) Applicant is enabled for the construction of PCR reagents.

(i) Applicant's rebuttal regarding the unpredictability of using vectors. It is noted that applicant has drawn a distinction between "viral therapy" and "gene therapy". However, the administration of a virus comprising DNA *in vivo* is considered gene therapy and is subject to the unpredictable factors discussed above.

(3) Claim 34 is directed to a cell transformed with a selectively replicating viral vector and is enabled for such (*in vitro*) as is taught in the specification.

(4) Claims 35 and 36 directed to pathway responsive promoters selected from group consisting of PAI and SRE, is enabled, as applicant has taught how to make the

aforementioned promoters, and is stated under the scope of enablement under the statement of rejection of this action.

In summary, all rebuttals made by applicant regarding rejections made in FOAM, are argued above.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claim 35 is rejected under 35 U.S.C. 102(e) as being anticipated by Buckbinder et al.

Claim 35 is directed to a p53 pathway-responsive promoter selected from the group consisting of p53CON and RGC.

Buckbinder et al. taught the RGC p53 binding sequences and experiments that an exogenous promoter carrying a p53 reponsive element is responsible for pronounced induction of the endogenous hdm-2 gene in a p53 dependent manner. Therefore, Buckbinder et al. taught the elements as claimed in the instant application. (See col. 15 lines 50-65 and col. 16 lines 1-12.).

7. Claim 36 is rejected under 35 U.S.C. 102(e) as being anticipated by Grainger et al. (US. Pat No: 6,117,911).

Claim 36 is directed to a TGF-beta pathway responsive promoter selected from a group consisting of PAI and SRE.

Grainger et al. taught that a mammal exhibiting a reduced level of TGF-beta might be due to various factors one of which is the presence of a 4G allele of the PAI-1 promoter. They also measured the PAI-1/TGF-beta response to fat feeding. (See vol. 33 lines 23-37). Therefore, Grainger anticipated all the elements as claimed in the instant application.

8. Any rejections not reiterated in this action have been withdrawn.

Conclusion

9. Claims 1-40 are rejected.

10. Any inquiry concerning this communication should be directed to Eleanor Sorbello, who can be reached at (703)-308-6043. The examiner can normally be reached on Mondays-Fridays from 6.30 a.m. to 3.00 p.m. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Deborah Clark

DEBORAH J.R. CLARK
PRIMARY EXAMINER